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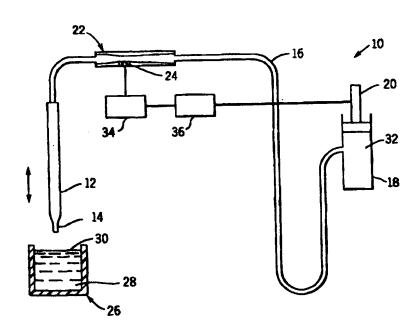
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(57) Abstract

Methods of fluid handling are disclosed. According to one method, a tip of a nozzle is moved below a surface of the fluid to be handled. A pump fluidly associated with the nozzle is energized to move fluid into the nozzle. A pressure transducer fluidly associated with the nozzle is energized to monitor pressure within the nozzle. Pressure within the nozzle is substantially continuously monitored with the pressure transducer during operation of the pump. Based on the substantially continuously monitored pressure within the nozzle, it is determined whether movement of fluid into the nozzle is intended or unintended. Similar methods may be used to move fluid out to the nozzle.

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FLUID HANDLER AND METHOD OF HANDLING A FLUID

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5 BACKGROUND OF INVENTION

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Embodiments described herein relate generally to handling a fluid automatically. More specifically, the embodiments relate to moving a fluid into and out of a nozzle.

Fluid handlers or generally mechanisms for moving a fluid have many applications. One such application involves a type of machine referred to as an automated medical analyzer. These analyzers perform medical tests on a sample, such as blood, urine and the like. These tests may require mixing of the sample with a fluid. Once the sample is mixed with the fluid, a chemical reaction may take place. The chemical reaction can be used to provide a medical professional with medical information about the sample. Because the sample may have come from a human patient, the medical information about the sample may provide the medical professional with information about the patient's medical condition.

For these analyzers to operate as intended, and to give the correct medical information to the medical professional, it is desirable to mix only a specific amount of sample with a specific amount of fluid. If too much or too little sample, or

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if too much or too little fluid is used during the mixing process, then the chemical reaction between the sample and the fluid may not occur as desired. If this occurs, the test may give inaccurate medical information about the sample and about the patient. It may not be in the patient's best interests for a medical professional to be given inaccurate medical information. Therefore, it is desirable to provide a fluid handler which can alert an automated medical analyzer operator when the wrong amount of sample and/or fluid has been used with a particular medical test.

SUMMARY OF INVENTION

Methods of fluid handling are disclosed. According to one method, a tip of a nozzle is moved below a surface of the fluid to be handled. A pump fluidly associated with the nozzle is energized to move fluid into the nozzle. A pressure transducer fluidly associated with the nozzle is energized to monitor pressure within the nozzle. Pressure within the nozzle is substantially continuously monitored with the pressure transducer during operation of the pump. Based on the substantially continuously monitored pressure within the nozzle, it is determined whether movement of fluid into the nozzle is intended or unintended.

According to another method, a tip of a nozzle is moved adjacent a container to receive the fluid. A pump fluidly associated with the nozzle is energized to move fluid out of the nozzle. A pressure transducer fluidly associated with the nozzle is energized to monitor pressure within the nozzle. Pressure within the nozzle is substantially continuously monitored with the pressure transducer during operation of the pump. Based on the substantially continuously monitored pressure within the nozzle, it is determined whether movement of fluid out of the nozzle is intended or unintended.

In yet a further method, a nozzle is located adjacent a container for the fluid. A pump fluidly associated with the nozzle is energized to move fluid with respect to the nozzle. A pressure transducer fluidly associated with the nozzle is energized to monitor transient pressure within the nozzle. Transient pressure within the nozzle is substantially continuously monitored with the pressure transducer during operation of the pump. Based on the substantially continuously monitored pressure within the nozzle, it is determined whether movement of fluid with respect to the nozzle is intended or unintended.

BRIEF DESCRIPTION OF DRAWINGS

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- Fig. 1 is a generic diagrammatic view of a fluid handler described herein;
- Fig. 2 is a block schematic diagram of a portion of the fluid handler shown in Fig. 1:
- Pig. 3 is a schematic diagram of a portion of the fluid handler shown in Fig. 2;
 - Figs. 4A and 4B display data obtained during intended operation of the fluid handler;
- Figs. 5A and 5B display data obtained during unintended operation of the fluid handler; and
 - Figs. 6A and 6B display filtered data obtained during operation of the fluid handler.

30 DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Embodiments described in detail below handle fluids. These embodiments can be used to handle, e.g. aspirate, dispense, mix, etc., any suitable fluid. While, for the sake of clarity of understanding, the embodiments are discussed with respect to

their employments in a medical analytical instrument, it is to be understood that the embodiments may be used in any appropriate employment. Also, regarding the methods of handling a fluid described below, it is to be recognized that the steps of one method may be performed in any suitable order and that steps from one method may be combined with steps from another method to yield yet additional methods. To more clearly identify operation of the fluid handler 10, both intended, i.e. correctly performed, and unintended, i.e. incorrectly performed, fluid handling operations of the fluid handler 10 will be 10 discussed. The fluid handler 10 is sufficient to detect unintended fluid handling operations due to factors such as clogs, clots, debris, bubbles, foam, etc. By detecting unintended fluid handling operations as they occur, it is possible to disregard tests involved without having to rely on 15 the possibility of the test result itself being out of range to indicate an unintended fluid handling operation. This can also reduce the probability of operator error.

Fig. 1 illustrates one embodiment of a fluid handler 10. This illustrated embodiment 10 comprises a nozzle 12 having a 20 tip 14 connected via a conduit 16 to a pump 18 operated by a prime mover 20. A pressure transducer 22 having a sensor 24 is fluidly connected with the conduit 16 between the nozzle 12 and the pump 18. The nozzle 12 may be movably supported by a suitably constructed gantry, not shown for clarity, so that the 25 nozzle 12 may move toward and away from a container 26 retaining a fluid 28 having a fluid surface 30. The nozzle 12, the conduit 16 and the pump 18 contain a liquid 32, such as distilled water, a buffer, and the like, which facilitates aspiration and dispense of fluid 28. Thus, the pressure 30 transducer 22 is "in line" with the liquid 32. To control and to monitor operation of the fluid handler 10, the pressure transducer 22 is electrically connected with operational electronics 34 which are, in turn, electrically connected with a controller 36. The controller 36 is electrically connected with 35

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the prime mover 20 of the pump 18 so that the pump 18 and the operational electronics 34 can operate in unison.

In one particular construction of the fluid handler 10, the nozzle 12 is a rigid aspiration probe. This probe has an inner diameter of about 0.04 inches, a length of about 7 inches, and a tip with an inner diameter of about 0.014 inches and a length of about 0.278 inches. In this construction, the conduit 16 is made of a polymer of low compliance, such as TEFZEL tubing (available from Du Pont Co., Wilmington, DE), with an inner diameter of about 0.063 inches. If it is desirable to minimize damping of transient pressure variations, then the axial length of the conduit 16, particularly between the nozzle 12 and the pressure transducer 22, should be minimized or rendered as short as practical. In one construction, the pressure transducer 22 may be a TransPac IV, manufactured by Abbott Laboratories, Salt 15 Lake City, UT. Generally, the pressure transducer 22 should be capable of sensing rapid transient pressure changes within a range of at least about -2 to about 6 psig, and particularly should have an overpressure capability to about 100 psig to enable effective washing of the nozzle 12. The pressure 20 transducer 22 should have a fast response time, up to about 10 The pressure transducer 22 monitors pressure within the conduit 16 substantially continuously (at least about 1000 times per second in one embodiment), thereby monitoring transient conduit 16 pressures, which allows unintended aspirations and 25 dispenses to be indicated almost immediately. construction, the pump 18 is a syringe pump, such as a Cavro 3000 (Cavro Scientific Instruments Inc., Sunnyvale, CA). It is to be recognized that these specific constructions and others below are given for the sake of facilitating understanding. 30

A description of a particular construction of the operational electronics 34 follows with reference to Figs. 2 and However, it is emphasized that this is only one possible construction for controlling operation of the fluid handler 10. For instance, portions of the operational electronics 34 and/or

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its functions may be incorporated into a computer 38, provided in hardware or software form, etc.

As shown in Fig. 2, the pressure transducer 22 is electrically connected to an electronic buffer circuit 40 so that an electrical signal generated by the sensor 24 responsive to a pressure in the conduit 16 is transmitted to the buffer circuit 40. A detailed schematic of one embodiment of the buffer circuit 40 is illustrated in Fig. 3. The buffer circuit 40 of Fig. 3 includes a voltage source circuit 42 which supplies about 10 VDC to a bridge circuit 44 associated with the pressure transducer 22. An electrical output of the bridge circuit 44 is electrically connected to a differential amplifier circuit 46, which is also connected to an adjustable offset voltage generator circuit 48. An output of the differential amplifier circuit 46 is the output of the electronic buffer circuit 40. The output voltage of the differential amplifier circuit 46 can be expressed as:

$$V_{out} = (\frac{2R_2}{R_5 + R_6} + 2)(V_2 - V_1) + V_A$$

The output of the differential amplifier circuit 46 is electrically connected to an analog to digital converter 50. The analog to digital converter 50 may be provided as part of the computer 38 or as part of another computer. In another construction, the analog to digital converter 50 may be substantially similar to an ATMIO-16-L9 from National Instruments of Austin, TX.

In the illustrated embodiment, an output of the analog to digital converter 50 is electrically connected to a digital filter 52. In one embodiment, the digital filter 52 may be substantially similar to a digital lowpass filter, such as a digital Butterworth filter algorithm and the like. This algorithm may be performed by the computer 38. In a particular embodiment, the filter algorithm of the commercial software package MathCAD (available from MathSoft, Inc., Cambridge, MA)

may be used. In other embodiments, filtering may be performed by an analog filter incorporated into the buffer circuit 40 or some other digital filter performed by the computer 38.

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an output of the digital filter 52 is electrically connected to an error detector 54. The error detector 54 may be of any suitable construction, such as a software routine, a hardware configuration, an electrical circuit etc., that performs fluid handling error detection tasks as detailed below. In some embodiments, the error detector 54 may be part of the computer 38 or may be a separate signal processing device or microcontroller. The computer 38 or the error detector 54 may be electrically connected to the controller 36 to allow operation of the pump 18 to be responsive to a signal from the pressure transducer 22.

Further appreciation of the construction of the fluid handler 10 may be obtained with a discussion of the operation of the fluid handler 10. This discussion is provided for clarity of understanding.

According to one method of operation, referring to Figs. 1 through 3, liquid 32 fills the nozzle 12, the conduit 16, the 20 pressure transducer 22 and the pump 18. In some cases, the pump 18 may move the liquid 32 within the fluid handler 10 such that a volume, about 5 to 10 μ l, of ambient air may be located within the nozzle 12 adjacent the tip 14. This volume of air may be used to separate fluid 28 aspirated from the container 26 into 25 the nozzle 12 and the liquid 32 already present in the nozzle This procedure can also be used to "stack" different fluids 28 within the nozzle 12. In essence, a first fluid 28, such as sample, is aspirated (discussed below) into the nozzle 12 and is separated from the liquid 32 by the first air volume. 30 second fluid 28, such as a reagent, is aspirated into the nozzle 12, a second air volume separates the second fluid 28 from the first fluid 28. Then, the first and second fluids 28 can be dispensed from the nozzle 12 into the same of a different

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container 26, such as a reaction vessel. This procedure can be used to increase throughput.

To handle fluid 28, the nozzle 12 is moved by a suitable prime mover, not shown for clarity, towards the surface 30 of the fluid 28 to be handled. The nozzle 12 is moved so that the tip 14 of the nozzle 12 is offset sufficiently below the surface 30 of the fluid 28 within the container 26. An appropriate level sense mechanism, such as an R-F level sense, a capacitive level sense, a pneumatic level sense and the like, may be operatively associated with the nozzle 12 to facilitate automated detection of the surface 30 of the fluid 28. The distance of the offset between the surface 30 of the fluid 28 and the tip 14 of the nozzle 12 may vary depending upon fluid characteristics, level sense mechanism employed, ambient conditions, etc.

Once the tip 14 of the nozzle 12 is sufficiently offset below the surface 30 of the fluid 28 within the container 26, the controller 36 energizes the prime mover 20 associated with the pump 18. Substantially simultaneously, the controller 36 also energizes the pressure transducer 22. The pump 18 moves or aspirates a desired amount of fluid 28 from the container 26 and into the interior of the nozzle 12. As the fluid 28 passes from the container 26 into the interior of the nozzle 12, the sensor 24 of the pressure transducer 22 constantly measures pressure within the conduit 16 and detects a transient pressure change caused by flow of fluid 28 and liquid 32 within the nozzle 12 and the conduit 16 influenced by operation of the pump 18. signals energizing the prime mover 20 sent from the controller 36 to the prime mover 20 correspond to a signal expected to be received from the sensor 24. This facilitates analysis of the signal from the sensor 24.

Responsive to the pressure sensed by the sensor 24 of the pressure transducer 22, the bridge circuit 44 generates an electrical signal. The electrical signal generated by the bridge circuit 44 is sent to the differential amplifier circuit

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46 of the buffer circuit 40. The buffer circuit 40 produces an amplified electrical signal representative of an instantaneous pressure sensed by the sensor 24. The amplified electrical signal is fed into the computer 38. Once the amplified electrical signal is sent to the computer 38, the analog to digital converter 50 generates a digital signal corresponding to a voltage of the amplified electrical signal emitted by the buffer circuit 40. Thus, the digital signal is indicative of the pressure sensed by the sensor 24. The digital signal may be filtered by the digital filter 52. The filtered signal is processed by the error detector 54 which monitors a transient pressure signal to determine whether an intended aspiration has occurred. In one embodiment, the error detector 54 is enabled by a signal from the controller 36, indicating that aspiration has commenced and that the signal from the sensor 24 should be monitored for indication of errors or unintended aspirations.

The illustrated embodiment of the fluid handler 10 may also be used to monitor dispense of fluid 28 from the nozzle 12 into the container 26 or some other fluid receiver, such as a reaction vessel and the like. Substantially similarly to the above-described steps, a fluid 28 dispense is initiated by operation of the pump 18. The error detector 54 is enabled by the controller 36 substantially simultaneously with the pump 18. The error detector 54 monitors the signal, which is indicative of the pressure sensed by the sensor 24, sent by the sensor 24 and processed by the operational electronics 34 to determine whether an intended dispense has occurred.

Several methods exist for using the signal, indicative of pressure sensed by the sensor 24, sent from the sensor 24 to determine whether an intended aspiration and/or dispense has occurred based on transient pressure signals sent by the sensor 24. Some of these methods are described in the following examples. It is to be noted that these examples are provided for clarity of understanding.

In the examples, data were collected using an embodiment of the fluid handler 10 which is substantially similar to that described above. Fluid 28 volumes of about 50 μl were aspirated into the nozzle 12, with fluid 28 flow accelerated at a substantially constant rate of about 1563 μ l/sec/sec until 5 steady state flow rate of about 83 μ l/sec was reached. deceleration was also substantially constant at about 1563 μ l/sec/sec. Dispenses of about 40 μ l were also measured, with a steady flow rate of about 391 μ l/sec and flow acceleration and deceleration rates of about 26.040 μ l/sec/sec. The operational 10 electronics 34 were adjusted (gain, threshold, etc.) so that an electrical signal presented to the analog to digital converter 50 is about 0 volts prior to aspiration and does not saturate the operational electronics 34 during an intended aspirate/dispense cycle, which comprises aspiration of the 15 desired amount of fluid 28 into the nozzle 12 and dispense of a desired amount of fluid 28 from the nozzle 12. A common gain of the operational electronics 34 is about 9.6 V / psi. A representation of MathCAD software used to collect and to analyze the data in these examples is presented in Appendix A. 20

Example 1 - Intended Aspiration and Dispense profiles

About 50 μl aspiration and about 40 μl dispense of pig

25 serum were performed with the flow parameters as listed above.

The analog pressure signal from the sensor 24 was sampled substantially continuously at a rate of about 1000 samples/second and stored as unfiltered numerical data representing the instantaneous pressure profiles sensed by the 30 sensor 24 during both aspiration and dispense of fluid 28. The results of 5 repetitions of this experiment are presented in Fig. 4A (5 aspirations) and Fig. 4B (5 dispenses). These Figures demonstrate repeatability of the pressure sensing method. The pressure spikes immediately preceding and following 35 the aspiration and dispense were artificially imposed on the

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data to facilitate extraction and display of the pressures during actual aspiration and dispense. A representation of MathCAD software used to extract the pressures during aspiration and dispense is found in Appendix A, section 2. From this, it is apparent that an instantaneous pressure profile derived from data obtained by the sensor 24 can be compared to a predetermined pressure profile to conclude whether the fluid handling operation involved was intended or unintended.

Example 2 - Unintended Aspiration and Dispense 10

Interrupted aspiration of pig serum was performed by removing the container 26 from the nozzle 12 during an about 50 µl aspiration, resulting in partial aspiration of air. dispense portion of the aspirate/dispense cycle consequently also included partial dispense of air. Instantaneous pressure profiles of 5 unintended aspirations and dispenses were produced as in Example 1 and are illustrated in Fig. 5A (5 aspirations) and Fig. 5B (5 dispenses). Varying amounts of air were aspired during the unintended aspirations. A representation of the 20 MathCAD software used to extract the pressures during the unintended aspiration and dispense is found in Appendix A. section 3.

Example 3 - Digital Filtering of Pressure Profiles 25

The pressure profile data acquired as described in examples 1 and 2 was filtered with a MathCAD digital Butterworth filter described above. This is a 31 coefficient digital lowpass 30 filter with a cutoff frequency of about .01 times the sampling frequency (or about 10 Hz). A representation of the MathCAD software used to execute this filtering is found in Appendix A, section 4. The results of this filtering are illustrated in Fig. 6A (5 intended and 5 unintended aspirations) and Fig. 6B (5 intended and 5 unintended dispenses). The unintended

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aspirations and dispenses are clearly distinguishable from the intended aspiration and dispense profiles.

Example 4 - Error Detection by Integration

Intended and unintended filtered and unfiltered pressure profile data was integrated as an exemplary error detection method. The integration was mathematically performed with MathCAD software (represented in Appendix A, sections 2, 3, and 5). The results of the integration are presented in Table 1. The integration results for the intended aspirations and dispenses are statistically distinguishable from those of the unintended aspirations and dispenses. This method is, however, sensitive to fluid viscosity (which may range from about 1 to about 14 centipoise) and accordingly is less desirable for small aspiration and dispense volumes (on the order of about 10 μ l).

15 Example 5 - Error Detection by Mean Pressure Difference

Five consecutive data points were sampled from each of the filtered intended and unintended aspiration pressure profiles immediately prior to syringe deceleration, so that they represent pressure sensed by the sensor 24 during steady-state. 20 Five consecutive data points were also sampled following completion of aspiration. The difference between the mean pressure during steady state aspiration and the mean pressure following completion of the aspiration was calculated and compared to a tolerance band. In this example, executed by the 25 software represented in Appendix A, section 7, the tolerance band was from about 0.35 to about 0.55. As shown in Table 2, the intended aspirations yielded mean pressure differences within the tolerance band, while the unintended aspirations yielded pressure differences outside the band. 30

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Example 6 - Error Detection by Variation of Pressure Difference from Mean

Data points from each of the filtered intended and unintended aspiration pressure profiles that fell within the steady state aspiration region were used to calculate the instantaneous difference between the pressure sensed by the sensor 24 at any time and the pressure sensed following completion of the aspiration. Each of these values was compared to the mean difference between the pressure during steady state aspiration and the pressure following aspiration (calculated as in Example 5). The number of times that the instantaneous pressure difference differed from the mean pressure difference by more than a specified tolerance was counted. In the case of the software represented in Appendix A, section 7, the tolerance band was about 0.1 on either side of the mean difference. As shown in Table 3, the intended aspiration profiles had uniformly zero deviations outside of the tolerance band, while the unintended aspirations had numerous such deviations.

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The error detection methods presented in Examples 4 through 6 are just four of the many possible methods to detect unintended aspirations and dispenses from the pressure profiles measured by the sensor 24. In some embodiments, several error detection methods may be combined. The Examples demonstrate that the pressure data collected by embodiments of the fluid handler 10 may be used in an aspiration and dispense error detection method.

The pressure profiles of intended and unintended aspirations and dispenses are directly affected by the acceleration and deceleration profiles of the pump 18. For instance, a uniform ramp acceleration and deceleration of the pump 18 will result in pressure values that do not reach steady state. It is possible to modify the acceleration and deceleration profiles of the pump 18 to yield intended and

unintended aspiration and dispense pressure profiles that may be more easily or reliably distinguished by these or other error detection schemes. In other embodiments, feedback from elements, other than the pressure transducer 22, of the fluid handler 10, such as movement of the pump 18, fluid surface 30 level sense information, etc., alone or in combination with each other or with the pressure transducer 22 information, can be used to provide an indication of intended or unintended fluid handling operations.

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Table 1: Error Detection by Integration of Pressure

	Integrated Pressure Values				
Filtered	Aspiration		Dispense		
	Intended	Uninte nde d	Int ende d	Unintended	
	1268	1020	438	145	
	1287	1047	448	154	
	1282	1212	443	321	
	1272	1099	442	167	
	1285	1166	439	225	
Unfiltered	Aspiration		Dispense		
	Intended	Unintended	Intended	Unintended	
	1212	787	774	238	
	1241	829	787	253	
	1233	1114	778	568	
	1216	919	772	266	
	1236	1033	771	399	

Table 2: Error Detection by Mean Pressure
Difference

	Mean pressure difference		
I	ntended	Un:	intend e d
0.496	Within tolerance	0.141	Outside tol eranc e
0.528	Within tolerance	0.169	Outside tolerance
0.517	Within tolerance	0.225	Outsi d e toler an ce
0.501	Within tolerance	0.185	Outside tolerance
0.509	Within tolerance	0.230	Outside tolerance

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Table 3: Error Detection by Variation of Pressure Difference from Mean

Number of points outside tolerance band		
Intended	Unintended	
0	78	
0	82	
0	378	
0	110	
0	233	

APPENDIX A

Section 1

The following document is the data associated with a TransPac IV pressure transducer placed in-line with the aspirate/dispense probe.

The test setup consisted of:

bubbles were removed from the tubing, syrings, and transducer. The excitation voltage for the tranducer 1. Transpac IV pressure transducer connected in line with the probe with a DI water working fluid. All was 10V. Therefore the reponse is 0.0025V/psl unamplified.

2. The Thela Z Breadboard system uses OMS Indexers and IMS Drivers (Microstopping). This system 3. The tubing from the transducer to the probe and syringe to the transducer was changed from operated at 32,000 steps = 1 Inch.

(0.030" (D) to (0.063" ID).

4. A Cavro syringe was used with a 250d syringo. 5. The gain on the pressure transducer was reduced.

```
Test Run Tube = 1 Asp Volume = 5000 Disp Volume = 4000 Test Cycle Count = 5
Theta (X) Vel. = 6000 Theta (X) Acl = 32000
Disp Car.(Y)Vel = 20000 Disp Car.(Y)Acl = 50000
                                =985110
            = 25518 Z Acl
Z Vel
Z Vel (liquid sense) = 25518 Z Acl (liquid sense) = 1500000
Asp. Thete Position = 20 Asp. Liquid Sense Over = 0 Asp Max Z down = 25000
Liquid Sense Cain I OFF
Liquid Sense Gain 2 ON
Liquid Sense Gain 3 ON
Aspirate Cosine Ramp OFF
Disp. Theta Position = -2486 Disp. Liq. Sense Over = 1 Disp. Max Z down = 4000
Tests Were Run with SCALE Mode
AND taking weight measurements - 2nd weight Dolay = 5
Dispense Cosine Ramp OFF
Wash Theta Position = -1827 Wash Max Z down = 3600
Princing Syr. Steps = 0
Priming Vel. Draw = 25000 Priming Acl. Draw = 200000
Priming Vel. Dispense = 60000 Priming Acl. Dispense = 200000
 Priming Syr. Overdrive = 0
Syr. Valve In Steps = 1080 Syr. Valve Bypass Steps = 2150 Syr. Valve Out Steps = 0
Syr. Valve Vel = 20000 Syr. Valve Acl = 100000
  Cycles to run prime = 5
 Syr. Vel. Draw = 16000 Syr. Acl. Draw = 300000
 Syr. Vel. Dispense = 75000 Syr. Acl Dispense = 5000000
 Syringe Resolution = 48000 Syringe Size = 250
 Syringe overdrive = 2950
 Syr. Base Vol. Draw = 0 Syr. Base Vol. Dispense = 0.
 Int. Probe Wash Vel = 40000 Int. Probe Wash Acl. = 500000
 Int. Probe Wash Cycles = 27500
 Gilson Wash Vel. = 28000 Gilson Wash Acl. = 500w00
 Oileon Wash Cycles = 10000
 Delay to external wash = 50 Delay to internal wash = 0 Delay at wash bottom = 900
 Save Data Asp. Points = 10000 Save Data Dis. Points = 0
 Asp. Delay 1 = 200 Asp. Delay 2 = 100 Disp. Delay 1 = 400 Disp. Delay 2 = 100
 Pre-Asp Air Gap = 1920 Post_Asp Air Gap = 0
  .... Full Cycle Timing (in Mscc) -Last Run ....
  Theia is Aspirate = 515
```

Theta to Aspirate = 515

Z down Aspirate = 697 Syringe Aspirate = 882 Z Up Aspirate = 851

Theta to Dispense = 669

Z Down Dispense = 205 Syringe Dispense = 551 Z Up Dispense = 301

Theta to Wash = 332

Wash Down Cycle = 190 Wash Up Cycle = 1088 To End of Cycle = 1

Total Cycle Time = 6282

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APPENDIX A

Section 2

Asp Vei = 16,000 Asp. Acc = 300,000
Disp Vei = 75,000 Disp Acc = 5,000,001
Aspirate Volume = 50ul of Pig Serum Fluid
Dispense Volume = 40ul of Pig Serum Serum Fluid.

Press := READPRN(vvt01s000)

Pri := Press

N1 := last(Pr1)

NI =6.294-103

i := 0..NI

Weight1 := 40.77

Press2 = READPRN(vvt01e001)

Pr2 = Press2 <5>

N2 := last(Pt2)

 $N2 = 6.342 \cdot 10^3$

j = 0..N2

Weight2 := 40.78

Press3 := READPRN(vvt01a002)

Pr3 = Press3 <0>

N3 := last(Pr3)

 $N3 = 6.326 \cdot 10^3$

k = 0..N3

Weight3 := 40.76

Press4 := REAUPKN(vvi01s003)

Pr4 :=. Press4 <0>

N4 := last(Pr4)

 $N4 = 6.334 \cdot 10^3$

1:= 0..N4

Weight4 := 40.72

Press5 := READPRN(vvt01a004)

Pró = Prසාර ^{4)>}

N5 := Lest(Pr5)

NS = 6.345·103

m:= 0.. N5

Weight5 := 40.77

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$$\begin{aligned} &\Pr{2}_{i+20} := \text{unfil} \left(9.99 - \Pr{2}_{i+20}, 0\right), \\ &\Pr{2}_{i+20} := \text{last} \left(\Pr{2}\right) & \text{I2}_{i} := \text{last} \left(\Pr{2}\right) & \text{I3}_{i} := \text{last} \left(\Pr{2}\right) \\ &\text{I3}_{i} := \text{last} \left(\Pr{2}\right) & \text{I3}_{i} := \text{last} \left(\Pr{2}\right) & \text{I3}_{i} := \text{last} \left(\Pr{2}\right) \\ &\text{Pr}{2}_{ij} := \text{until} \left(9.99 - \Pr{2}_{ij}, 0\right) & \text{Pr}{3}_{ik} := \text{until} \left(9.99 - \Pr{3}_{ik}, 0\right) \\ &\text{I2}_{2} := \text{last} \left(\Pr{2}\right) & \text{I2}_{2} = 2.116 \cdot 10^{3} \\ &\text{I3}_{2} := \text{last} \left(\Pr{2}\right) & \text{I3}_{2} = 2.117 \cdot 10^{3} \\ &\text{lik} := \text{I3}_{2} + 1 ... \text{N3} \\ &\text{Pr}{2}_{ijj} := \text{I2}_{2} + 1 ... \text{N3} \\ &\text{Pr}{2}_{ijj} := \text{I2}_{2} + 1 ... \text{N3} \\ &\text{Pr}{3}_{ikk} := \text{until} \left(9.99 - \Pr{3}_{ikk}, 0\right) \\ &\text{I3}_{3} := \text{last} \left(\Pr{3}\right) & \text{I3}_{3} = 4.277 \cdot 10^{3} \\ &\text{lik}_{4} := \text{I3}_{3} + 1 ... \text{N3} \\ &\text{liij} := \text{I2}_{3} + 1 ... \text{N3} \\ &\text{liij} := \text{I2}_{4} +$$

$$i22 = 51$$

$$Pr4d = 1.216 \cdot 10^{3}$$

$$JJ4b := J44 - J43$$

$$JJ4b + 50$$

$$Pr4e := \sum_{i22 = 51}^{1} Pr4c_{i22}$$

$$Pr4e = 772.231$$

Pr5d =
$$1.236 \cdot 10^3$$

JJ5b := J54 - J53

JJ5b + 50

Pr5e := $\sum_{i22 = 51}^{i22 = 51}$ Pr5e = 771.079

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APPENDIX A

section 3

Asp Vel = 16,000 Asp. Acc = 300,000

Disp Vel = 75,000 Disp Acc = 5,000,000

Aspirate Volume = 50ul of Pig Serum with a break in fluid contact during aspiration Dispense Volume = 40ul of Pig Serum available

Press8 = READPRN(vvt01d002) Press9 = READPRN(vvi01d003)

Pr8 := Press8 Press9 Pr9 := Press9 Press9 Pr8 := last(Pr8)

N8 := last(Pr8)

N9 := last(Pr9)

N9 = 6.185-10 Press9 Press9

Weight9 := .23

Weight8 := 23.68

Press10 = READPRN(vvt01d004)

Pr10 := Press10<0>

N10 := lest(Pr10)

N10 =6.328-10³

m := 0..N10

Weight10 := 10.75

SUBSTITUTE SHEET (RULE 26)

Priod = 1.033-10³

JJ10b := J104 - J103

JJ10b + 50

Prioe :=
$$\sum_{i22=51}^{2} Prioe_{i22}$$

Prl0e = 399.219

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APPENDIX A

```
Pribso = Pribso
                            Prlb_112_ J11 + 50 := Prlb_112_ J11 + 49
     Pr2b30 := Pr2b49
                            Pr2bj22 - J21 + 50 := Pr2bj22 - J21 + 49
     Pr3b30 := Pr3b49
                            Pr3b_D2_D1+50 := Pr3b_D2_D1+49
     Pr4650 := Pr4649
                            Pr4b142 - 141 + 50 = Pr4b142 - 141 + 49
     Probso = Probso
                            Pr5b132_151+50 = Pr5b132_151+49
    Prob_ > Prob_9
                           Probjez - 361 + 50 := Probjez - 361 + 49
    Pr7650 = Pr7649
                           Pr7b_172_171+50 = Pr7b_172_171+49
    Pr8b49 = Pr8b49
                           Pr8b_122_121+50 = Pr8b_122_121+49
    Pr9b50 = Pr9b49
                           Pr9b_192_191+50 = Pr9b_192_191+49
                           Pr10bnoz - not + 50 = Pr10bnoz - not +49
    Priobso - Priobso
      Prices := Prices
                              Pric112-111+50 = Pric112-111+49
      Pr2050 := Pr2049
                              Pr2cm_ni+50 := Pr2cm_ni+49
      Pr3c49 := Pr3c49
                              Pr3c, 11+50 := Pr3c, 12-11+49
      Pr4c50 := Pr4c49
                              Pr4c142 - J41 + 50 := Pr4c142 - J41 + 49
      PrSc50 := PrSc49
                              Proc<sub>152 - 151 + 50</sub> := Proc<sub>152 - 151 + 49</sub>
      Procso := Procso
                             Pr6c/62 - 161 + 50 := Pr6c/62 - 161 + 49
      Pr7c50 :- Pr7c49
                             Pr7c172 - 171 + 50 := Pr7c172 - 171 + 49
      Pr8c50 := Pr8c49
                             Pr8cj82 - J81 + 50 := Pr8cj82 - J81 + 49
      Pr9c50 := Pr9c49
                             Pr9c<sub>192-191+50</sub> := Pr9c<sub>192-191+49</sub>
      Pr10c50 := Pr10c49
                             Prioc_1102 - 1101 + 50 := Prioc_1102 - 1101 + 49.
cl := lowpess(.01,31)
Prelb := response(Prlb, cl, 2047)
                                           Prelo := responso(Pric.cl.2047)
Pre2b := response(Pr2b;c1,2047)
                                           Pre2c := response(Pr2c, cl, 2047)
Pre3b := response(Pr3b,cl, 2047)
                                           Pre3o := response(Pr3o,c1,2047)
Pro4b := response(Pr4b.cl.2047)
                                           Pre4c := response(Pr4c.ol.2047)
Prasb := response(Prsb,c1,2047)
                                           Presc := response(PrSc, c1, 2047)
Preob := response(Prob,c1,2047)
                                           Proof := response(Proof, 01, 2047)
Pre75 := response(Pr76,c1,2047)
                                           Pre7c := response(Pr7c,c1,2047)
PreSb := response(Pr8b,o1,2047)
                                           Presc := response(Prsc, cl, 2047)
Pre95 := response(Pr95,c1,2047)
                                           Pre90 = response(Pr9c, c1, 2047)
Pr=105 := response(Pr10b, c1, 2047)
                                           Pre10c := response(Pr10c;c1,2047)
```

PreId :=
$$\sum_{i22=51}^{50} (2 - PreIb)_{i22}$$
 Pre2d := $\sum_{i22=51}^{50} (2 - Pre2b)_{i22}$
Pre1d = 1.268-10³ Pre2d := $\sum_{i22=51}^{50} (2 - Pre2b)_{i22}$
Pre3d := $\sum_{i22=51}^{114+50} (2 - Pre3b)_{i22}$ Pre4d := $\sum_{i22=51}^{50} (2 - Pre4b)_{i22}$
Pre5d := 1.285-10³ Pre6d := $\sum_{i22=51}^{50} (2 - Pre6b)_{i22}$
Pre7d := $\sum_{i22=51}^{117+50} (2 - Pre7b)_{i22}$ Pre6d := $\sum_{i22=51}^{50} (2 - Pre6b)_{i22}$
Pre7d := $\sum_{i22=51}^{119+50} (2 - Pre7b)_{i22}$ Pre8d := $\sum_{i22=51}^{50} (2 - Pre8b)_{i22}$ Pre8d := $\sum_{i22=51}^{50} (2 - Pre8b)_{i22}$ Pre8d := $\sum_{i22=51}^{50} (2 - Pre8b)_{i22}$ Pre10d := $\sum_{i22=51}^{50} (2 - Pre10b)_{i22}$ Pre10d := $\sum_{i22=51}^{50} (2 - Pre10b)_{i22}$ Pre10d := $\sum_{i22=51}^{50} (2 - Pre10b)_{i22}$ Pre10d := $\sum_{i22=51}^{50} (2 - Pre10b)_{i22}$

APPENDIX A

Prele :=
$$\sum_{i22=51}^{JJ1b+50}$$
 Prele := $\sum_{i22=51}^{JJ2b+50}$ Prele = 438.093 Prele = 447.617

Pre3e =
$$\frac{JJ3b + 50}{572 = 51}$$
 Pre3e = $\frac{JJ4b + 50}{22 = 51}$ Pre4e = $\frac{\sum_{i22 = 51}}{22 = 51}$ Pre4e = 442.369

PreSe =
$$\sum_{i22=51}^{JJ5b+50} PreSe_{i22}$$
 PreSe = $\sum_{i22=51}^{JJ6b+50} PreSe_{i22}$
PreSe = 438.971 PreSe = 144.978

$$Pre7e = \sum_{i22=51}^{JJ8b+50} Pre8e := \sum_{i22=51}^{JJ8b+50} Pre8c_{i22}$$

$$Pre7e = 154.061$$

Pre9e :=
$$\sum_{i22=51}^{JJ10b+50} Pre9e_{i22}$$
 Pre10e := $\sum_{i22=51}^{JJ10b+50} Pre10e_{i22}$
Pre9e = 166.599 Pre10e = 224.558

APPRNDIX A

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Prd2_{i3} := Pr2b_{i3}
me2 := mean(Prd2) me2 = 0.931
k2_{i3} := if(Prd2_{i3} < me2 -
$$\alpha$$
, 1, 0)
k2b_{i3} := if[Prd2_{i3} > (me2 + α), 1, 0]
K2 :=
$$\begin{bmatrix} 49 \\ 15 = 0 \end{bmatrix}$$
K2 := 0

Prd3₁₅ := Pr3b₁₅

me3 := mean(Prd3) me3 = 0.952

k3₁₅ := if(Prd3₁₅ < me3 - er, 1, 0)

k3b₁₅ := if[Prd3₁₅ > (me3 + er), 1, 0]

K3 :=
$$\begin{bmatrix} 49 \\ \sum_{i,j=0}^{49} k3_{i,j} + k3b_{i,j} \end{bmatrix}$$

K3 = 0

Prd4_{is} := Pr4b_{is}

me4 := mem(Prd4) me4 = 1.064

k4_{is} := if[Prd4_{is}<(me4 - .ex).1.0]

k4b_{is} := if[Prd4_{is}>(me4 + ex).1.0]

K4 :=
$$\begin{bmatrix} 49 \\ 15 = 0 \end{bmatrix}$$

K4 :=
$$\begin{bmatrix} 49 \\ 15 = 0 \end{bmatrix}$$

PrdS_{iS} = PrSb_S

med := mean(PrdS) med = 0.938

kS_{iS} := if(PrdS_{iS} < meS - er, 1.0)

kSb_{LS} := if(PrdS_{iS} > (meS + er), 1.0]

KS :=
$$\begin{bmatrix} 49 \\ \sum_{iS=0}^{49} kS_{iS} + kSb_{iS} \end{bmatrix}$$
KS := 0

Prd7₁₅ := Pr7b₁₅

me7 := mean(Prd7) me7 = 0.948

k7₁₅ := if(Prd7₁₅ < me7 - er.1.0)

k7b₁₅ := if[Prd7₁₅ > (me7 + er).1.0]

K7 :=
$$\begin{bmatrix} 49 \\ 15 = 0 \end{bmatrix}$$

K7 := 0

Prd6_{i3} := Pr6b_{i3}
me6 := mean(Prd6) me6 = 0.97
k6_{i5} := if[Prd6_{i5}<(me6 - er),1,0]
k6b_{i5} := if[Prd6_{i5}>(me6 + er),1,0]

K6 :=
$$\begin{bmatrix} 49 \\ i5 = 0 \end{bmatrix}$$
K6 = 21

Prd8_{i5} := Pr8b_{i5}

me8 := mesn(Prd8) me8 = 1.045

k8_{i5} := if(Prd8_{i5} < me8 - er, 1, 0)

k8b_{i5} := if(Prd8_{i5} > (me8 + er), 1, 0]

K8 :=
$$\begin{bmatrix} 49 \\ \text{i5} = 0 \end{bmatrix}$$

K8 :=
$$\begin{bmatrix} 49 \\ \text{i5} = 0 \end{bmatrix}$$

K8 = 3

Prd10_{i5} := Pr10b_{i5}
me10 := mean(Prd10) me10 = 0.958
k10_{i5} = if(Prd10_{i5} < me10 - cr.1.0)
k10b_{i5} := if(Prd10_{i5} > (me10 + cr).1.0)
K10 :=
$$\begin{bmatrix} 49 \\ \text{k10}_{i5} + \text{k10}_{i5} \end{bmatrix}$$
K10 = 0

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APPENDIX A

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mid2 := (JJ2 - 100)

Da2₁₆ := Pre2b_{16+mid2}

me2 := Ref2 - mean(Da2)

me2 = 0.528

vvo2 := if((Lob2 := if((Ref2 - Pre2b_{b2})<(me2 - er).1.0]

d2b_{b2} := if((Ref2 - Pre2b_{b2})>(me2 + er).1.0]

D2 :=
$$\begin{bmatrix} JJ2 - 10 \\ b2 = m \end{bmatrix}$$
D2 = 0

Ref1 := Pre2b112 + 50

Ref4:= Pre4b₁₁₄₊₅₀
mid4:= (114 - 100)

Da4₁₆:= Pro4b_{16+mid4}
me4:= Ref4 - mean(Da4)
mo4 = 0.501
vvc4:= if((Lob4:= if[(Ref4 - Pro4b_{b4})<(me4 - ex),1,0]
d4b_{b4}:= if[(Ref4 - Pre4b_{b4})>(mo4+ex),1,0]

D4:=
$$\begin{bmatrix} 114-10 \\ b4=nn \end{bmatrix}$$
D4 = 0

WHAT IS CLAIMED IS:

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- 5 1. A method of handling a fluid, the method comprising the steps of:
 - (a) moving a tip of a nozzle below a surface of the fluid to be handled;
 - (b) energizing a pump fluidly associated with the nozzle to move fluid into the nozzle;
 - (c) energizing a pressure transducer fluidly associated with the nozzle to monitor pressure within the nozzle;
 - (d) substantially continuously monitoring pressure within the nozzle with the pressure transducer during operation of the pump; and
 - (e) determining whether movement of fluid into the nozzle is intended or unintended based on the substantially continuously monitored pressure within the nozzle.
 - 2. A method as defined in claim 1 further comprising the steps of:
 - (f) using a liquid to move fluid into the nozzle;and
 - (g) locating the pressure transducer in a path of the liquid between the pump and the nozzle.

- 3. A method as defined in claim 1 wherein the determining step (e) comprises the steps of:
- (i) determining an instantaneous pressure profile from the substantially continuously monitored pressure; and
- (ii) comparing the instantaneous pressure profile determined in (i) with a predetermined pressure profile for an intended fluid movement and for an unintended fluid movement.

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- 4. A method as defined in claim 1 wherein the determining step (e) comprises the steps of:
- (i) obtaining pressure profile data from the pressure transducer;

(ii) filtering the pressure profile data; and

- (iii) determining whether the fluid movement was intended or unintended based on the filtered data.
- 5. A method as defined in claim 1 wherein the determining step (e) comprises the steps of:
- (i) integrating pressure profile data obtained from the pressure transducer; and
- (ii) determining whether the fluid movement was intended or unintended based on the integrated data.

- 6. A method as defined in claim 1 wherein the monitoring step (d) comprises the steps of:
- (i) monitoring pressure prior to pump deceleration;
- (ii) monitoring pressure after fluid movement is complete.

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7. A method as defined in claim 6 wherein the
determining step (e) comprises the steps of:
(i) determining a mean of pressure monitored in 6
(i);
(ii) determining a mean of pressure monitored in 6
(ii);
(iii) calculating a difference between the mean of 7
(i) and the mean of 7 (ii); and

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- 8. A method as defined in claim 1 wherein the determining step (e) comprises the steps of:
- (i) filtering data obtained from the pressure transducer in (d);

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(ii) calculating a difference between pressure monitored by the pressure transducer at any time before or during fluid movement and pressure monitored by the pressure transducer after fluid has moved into the nozzle;

(iv) comparing the difference with a tolerance band.

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(iii) comparing the difference calculated in 8 (ii) to a mean pressure difference between pressure monitored during movement of fluid into the nozzle and pressure monitored after fluid has moved into the nozzle;

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(iv) counting times when the difference calculated in 8 (ii) differs from the mean pressure difference by more than a specified tolerance; and

(v) determining whether the fluid movement was intended or unintended based on the times counted in 8 (iv).

9. A method of handling a fluid, the method comprising the steps of:

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- (a) moving a tip of a nozzle adjacent a container to receive the fluid;
- (b) energizing a pump fluidly associated with the nozzle to move fluid out of the nozzle;
- (c) energizing a pressure transducer fluidly associated with the nozzle to monitor pressure within the nozzle;
- (d) substantially continuously monitoring pressure within the nozzle with the pressure transducer during operation of the pump; and
- (e) determining whether movement of fluid out of the nozzle is intended or unintended based on the substantially continuously monitored pressure within the nozzle.
- 10. A method as defined in claim 9 further comprising the steps of:
- (f) using a liquid to move fluid out of the nozzle; and
- (g) locating the pressure transducer in a path of the liquid between the pump and the nozzle.
- 11. A method as defined in claim 9 wherein the determining step (e) comprises the steps of:
 - (i) determining an instantaneous pressure profile from the substantially continuously monitored pressure;
- (ii) comparing the instantaneous pressure profile determined in (i) with a predetermined pressure profile for an intended fluid movement and for an unintended fluid movement.

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- A method as defined in claim 9 wherein the determining step (e) comprises the steps of: obtaining pressure profile data from the pressure transducer; (ii) filtering the pressure profile data; and (iii) determining whether the fluid movement was intended or unintended based on the filtered data. A method as defined in claim 9 wherein the 13. determining step (e) comprises the steps of: (i) integrating pressure profile data obtained from the pressure transducer; and (ii) determining whether the fluid movement was intended or unintended based on the integrated data. 14. A method as defined in claim 9 wherein the monitoring step (d) comprises the steps of: monitoring pressure prior to pump deceleration; and (ii) monitoring pressure after fluid movement is complete. A method as defined in claim 14 wherein the determining step (e) comprises the steps of: determining a mean of pressure monitored in 14 (i) (i): (ii) determining a mean of pressure monitored in 14 (ii):
- (iii) calculating a difference between the mean of 14(i) and the mean of 14 (ii); and(iv) comparing the difference with a tolerance band.

- 16. A method as defined in claim 9 wherein the determining step (e) comprises the steps of:
- (i) filtering data obtained from the pressure transducer in (d);
- (ii) calculating a difference between pressure monitored by the pressure transducer at any time before or during fluid movement and pressure monitored by the pressure transducer after fluid has moved out of the nozzle;
- (iii) comparing the difference calculated in 16 (ii) to a mean pressure difference between pressure monitored during movement of fluid out of the nozzle and pressure monitored after fluid has moved out of the nozzle;
 - (iv) counting times when the difference calculated in 16 (ii) differs from the mean pressure difference by more than a specified tolerance; and
 - (v) determining whether the fluid movement was intended or unintended based on the times counted in 16 (iv).

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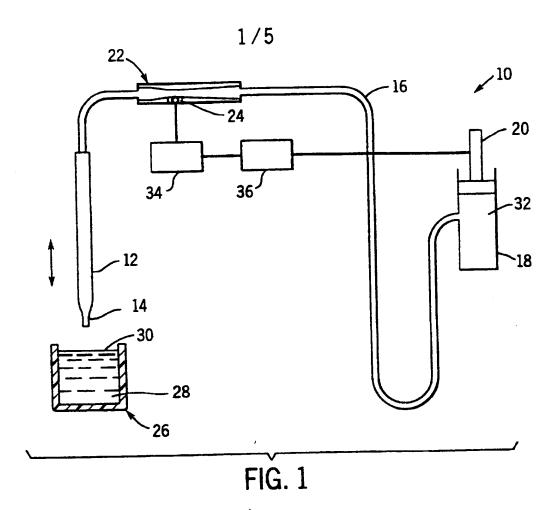
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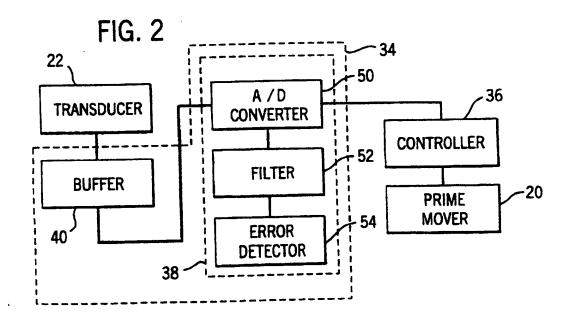
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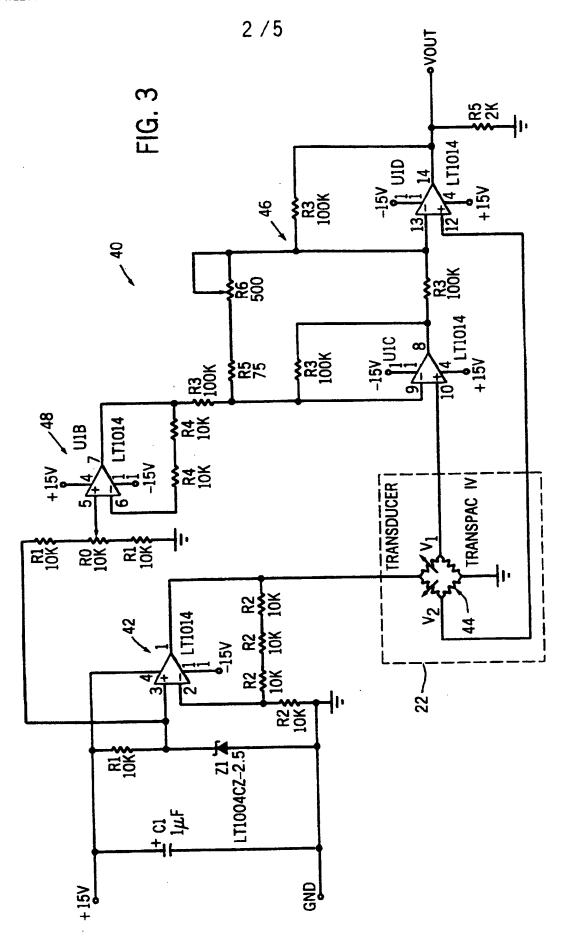
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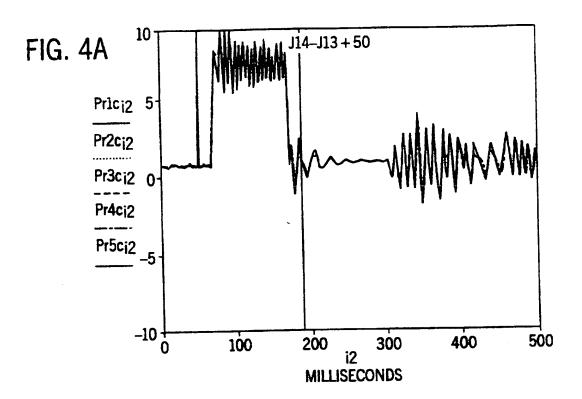
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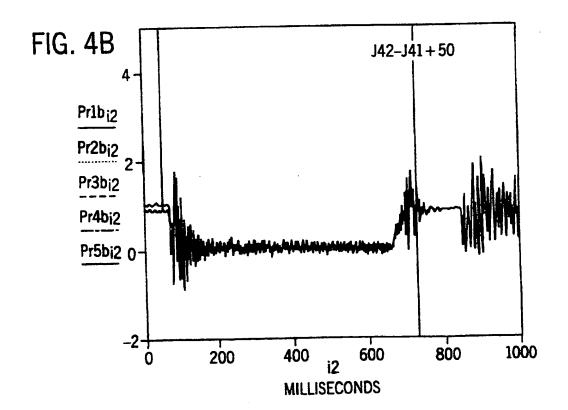
- 17. A method of handling a fluid, the method comprising the steps of:
- (a) locating a nozzle adjacent a container for the fluid;
- (b) energizing a pump fluidly associated with the nozzle to move fluid with respect to the nozzle;
- (c) energizing a pressure transducer fluidly associated with the nozzle to monitor transient pressure within the nozzle;
- (d) substantially continuously monitoring transient pressure within the nozzle with the pressure transducer during operation of the pump; and
- (e) determining whether movement of fluid with respect to the nozzle is intended or unintended based on the substantially continuously monitored pressure within the nozzle.
- 18. A method as defined in claim 17 further comprising the steps of:
- (f) moving a first fluid and a second fluid with respect to the nozzle; and
- (g) separating the first fluid and the second fluid within the nozzle with air.
- 19. A method as defined in claim 17 wherein the monitoring step (d) comprises monitoring transient pressure within the nozzle at least about 1000 times per second.
- 20. A method as defined in claim 17 wherein steps(b) and (c) are performed substantially simultaneously.

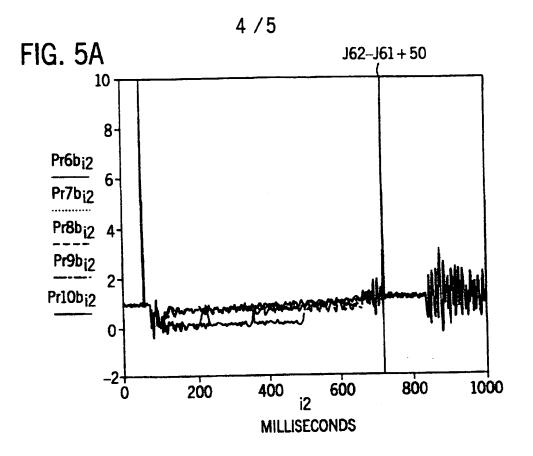


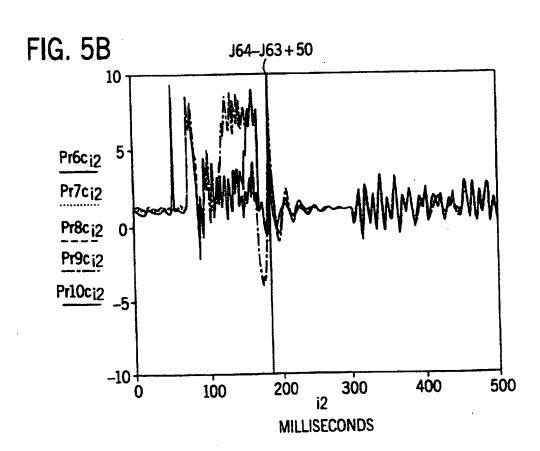


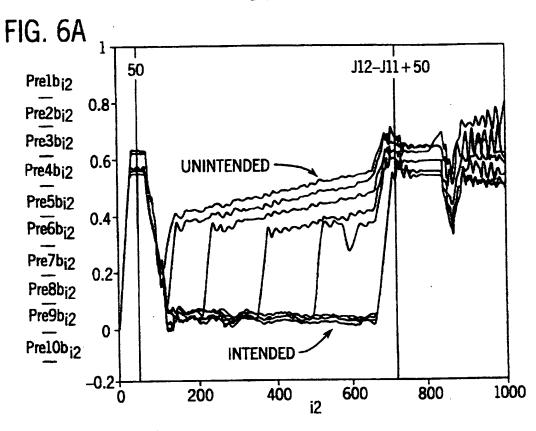


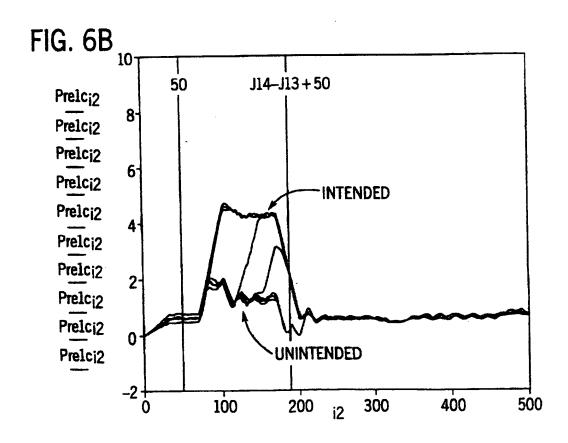


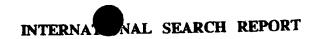












Nal Application No PCT/US 96/19329

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CLASSIFI	ICATION OF SUBJECT MATTER G01N35/10 G01F23/14 G01F1/34		
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cumentati	on searched other than minimum documentation to the extent that such	documents are included in the fields s	earched
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	l see column 5 line 44 - COLUMN 0.	illie 5	
	see column 6, line 30 - line 52; f 4A-4F	igures	·
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^	see column 4, line 11 - column 5,	line 16;	
	l figures 1-5		
	see page 6, line 24 - line 34 see page 9, line 3 - line 12		
	see page 9, line 20 - line 25		
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	figure 8		
		/ 	,
[V] E	urther documents are listed in the continuation of box C.	X Patent family members are his	ted in annex.
\Box		T later document published after the	international filing date
- 40-	awarnt defirms the general state of the art which is not	or priority date and not in consist cited to understand the principle	I MILL IDS TODITION OF
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·	er than the priority date claimed the actual completion of the international search	Date of mailing of the internation	nal search report
	16 April 1997		. 04, 97
Name a	and mailing address of the ISA	Authorized officer	
I	European Patent Office, P.B. 5818 Patentiaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,	Hocquet, A	
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INTERNATIONAL SEARCH REPORT

Inte onal Application No
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	see column 6, line 7 - line 21; figures 6,7,21 see column 7, line 62 - column 8, line 25;				
4	figure 6 WO 92 07241 A (DRD DILUTER CORP) 30 April 1992	2,10,18			
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